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Original Article

A randomised controlled trial of breathing modes for adaptive aerosol delivery in children with cystic fibrosis☆

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Abstract

Background: Aerosol delivery is a cornerstone of CF airways disease management. New nebulisers have reduced treatment times by utilising mesh technology for aerosol production. We have evaluated a further modification (target inhalation mode (TIM)) that may reduce treatment delivery times further.
Methods: Following a baseline period on tidal breathing mode (TBM), children with CF on long-term aerosol therapy were randomly allocated to either TIM, which optimises patient inhalations through a direct feedback mechanism, or to continue TBM. The primary outcome was nebuliser treatment times with secondary outcomes being adherence and patient preference.
Results: The ten children allocated TIM reduced their mean (SD) treatment times from 6.9(2.9) to 3.7(2.3) minutes ($p<0.001$). In contrast, treatment times were unchanged in the ten children allocated TBM. Mean adherence was maintained in the TIM group but declined in patients allocated TBM by >5%. All children preferred TIM to TBM.
Conclusion: TIM reduces nebuliser treatment times and may positively impact on adherence, although longer duration studies are required to examine this.
(ISRCTN65617839)

1. Introduction

Topical delivery of aerosolised therapies is an established treatment for chronic airway infection and inflammation in cystic fibrosis (CF).[1] Most drugs are delivered in an aerosolised form through a nebuliser and include antibiotics, Dornase alpha and hypertonic saline.[2,3] Recent innovations in nebuliser technology have resulted in improved delivery times and better airway deposition.[4] An additional feature of these new devices is the ability to record and examine the performance of the device by downloading stored data (electronic data capture).[5] In this way, CF teams are able to work with patients to optimise performance and support adherence.[5] The development of mesh technology facilitated the production of fine particle aerosols and realised the potential for adaptive aerosol delivery (AAD).[6] The concept of AAD is to time aerosol delivery with a certain phase of the respiratory cycle, by monitoring flow in and out of the mouthpiece. For the I-neb™ AAD device, a pulse of aerosol is generated during the mid/late phase of inspiration with a one

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second pause timed before expiration to avoid large airway deposition.[7] A recent innovation for the I-neb AAD device has been Target Inhalation Mode (TIM). [8] This provides direct feedback to the patient (through a vibrating mouthpiece), which encourages the patient to maximise inspiration. Radio-labelled aerosol studies have demonstrated improved lung deposition with TIM compared to standard tidal breathing mode (TBM).[9,10].

In this study, we have undertaken a randomised controlled trial to evaluate the impact of TIM compared to TBM on treatment times in a paediatric population. Treatment times and adherence were measured by electronic data capture.

2. Methods

2.1. Study design

This study was a randomised controlled trial comparing target inhalation mode (TIM) with standard tidal breathing mode (TBM) (ISRCTN65617839). The protocol was designed following CONSORT guidance.[11] The adaptive aerosol delivery (AAD) device was the I-neb™ (Respironics, Philips, Chichester, UK). After a baseline period of 4–6 weeks on TBM, patients were randomised to TIM or to continue TBM for 8–10 weeks (Appendix A). Computer generation of treatment allocation was by an independent researcher (not involved in the study) and concealed in opaque envelopes. A research physiotherapist (PMcC) undertook treatment allocation, instructed patients on the use of TIM and downloaded data. A researcher blinded to treatment allocation (PMcN) performed the data analysis. The primary outcome measure was average time for each treatment episode, calculated from data download. Secondary outcomes included treatment adherence (calculated as a percentage of expected treatments) and a patient preference questionnaire. Pulmonary function, adverse events and withdrawals were also recorded.

2.2. Participants

Clinically stable CF patients (5–16 years) attending the regional CF clinic at Alder Hey Children's Hospital were invited to participate in the study at their regular clinic visit. Inclusion criteria comprised all patients with *Pseudomonas aeruginosa* infection who were established on long-term (>3 months) antibiotic therapy through the I-neb™ using standard tidal breathing mode (TBM) of inhalation.

Patients with a pulmonary exacerbation in the previous four weeks were excluded. Pulmonary exacerbations were defined as an increase in cough, sputum production and/or a reduction in Forced Expiratory Volume in one second (FEV_1) greater than 10% of the previously recorded value.

At enrolment, patient demographics and clinical characteristics including their clinical status, most recent sputum/cough swab microbiology and annual review results (including pulmonary function tests, Northern Chest X-ray Score, and Schwachman score) were documented.

2.3. Patient preference questionnaire

At the final study visit patients randomised to TIM were asked to fill in a patient preference questionnaire. With the help of their parents they were asked to rate the answer from "completely agree" to "completely disagree" (Appendix B).

2.4. Treatment regimens

Treatment regimens were not changed during the study period (including the baseline). A commercial preparation of colistin was used (Promixin®, Profile Pharma Ltd., Chichester, UK) with a standard treatment dose being 1 MU (mega unit) diluted in 2 ml normal saline (1 ml being used for each of two daily treatments). In some patients, a once daily dose of 1 MU colistin in 1 ml normal saline was prescribed. Dornase alfa (Pulmozyme®) was also prescribed in several patients once daily.

2.5. Breathing modes for the AAD device

2.5.1. Tidal breathing mode (standard technique)

Tidal breathing mode delivers aerosol particles of medication during normal tidal breathing. The *I-neb*™ monitors and analyses the patient's first three breaths to determine breathing pattern and then delivers a timed pulse of aerosol during the mid-phase of the next inspiration. Throughout the treatment, each pulsed delivery of aerosol continues to be based on the breathing pattern of the preceding three breaths. The device calculates the volume of each inhalation and once the pre-programmed total dose of drug is delivered, gives audio and visual feedback informing the patient that treatment is complete. This is the standard method of drug delivery for the *I-neb*™.

2.5.2. Target inhalation mode (proposed intervention)

A high resistance mouthpiece guides the patient to use slower and deeper inhalations. The patient is encouraged to lengthen each inhalation by a vibratory feedback on the lip, which is the signal to exhale. Target inhalation mode guides the patient into taking the longest inhalation they can manage by gradually increasing the time from the beginning of each breath to the vibration. Once the maximum length of inhalation has been found (i.e. when the patient is unable to reach the vibration), the time is then shortened to a comfortable level for the patient and remains at this level until the preset dose is achieved. Visual and audio feedback will inform the patient that treatment is complete.

2.6. Data download

Electronic data capture was undertaken at each study visit using a docking station for the I-neb™ device and software provided by the company (*Insight system software*, Philips, Chichester, UK). Device performance was assessed at enrolment and new equipment provided for all patients (mesh plate and mouth piece). A training programme within

the Insight software package was also used to optimise breathing technique for each patient. Data were downloaded at each study visit (end of baseline/randomisation, visit 2 and end of study, visit 3). At the end of the study, patients allocated TBM were offered TIM. Percentage adherence was defined as the number of treatments taken/number of prescribed treatments x100.

2.7. Data analysis

Data were analysed using both paired-samples *T* test (for within patient comparisons) and Independent-samples *T* test (for relative change in outcomes over the study period between groups). We used SPSS 17.01 and all statistical tests were two-tailed with a p value equal to or less than 0.05 considered statistically significant. Sample size was informed by the standard deviation of treatment time in a previous study,[5] incorporating guidance on the design of a pilot explanatory study.[12].

2.8. Ethics

Study was approved by Alder Hey Children's NHS Foundation Trust Research Review Committee and the National Research Ethics Committee.

3. Results

Recruitment to the study was from July 2009 to April 2010. Twenty children were assessed for eligibility and allocated an intervention. None were excluded or lost to follow-up.

3.1. Patient characteristics

10 patients (7 male) were randomised to TIM and 10 (7) continued on TBM. All patients completed the study and data were analysed on an intention to treat basis (Appendix C).

The patients were prescribed 1–3 treatments a day. *Pseudomonas aeruginosa* was isolated from 7 patients in each group during their study participation. Baseline characteristics between the two groups were similar (Table 1). Average (SD) duration of the baseline period was 6 (2.2) weeks and for the intervention period, 8.3 (2.2) weeks.

One patient, in the TIM group, had an intermittent fault identified with his base unit and this was replaced during the course of the study.

3.2. Outcome measures

Mean (SD) treatment times were not significantly different between the two groups at baseline (TBM, 6.9 (3.0); TIM 6.9 (2.9) minutes). Patients allocated TIM had a significant reduction in treatment time to 3.7 (2.3) minutes ($p<0.001$) over the study period, whereas treatment times in the TBM group were maintained (7.3 (3.2) minutes) (Fig. 1).

Mean (SD) adherence was not significantly different between the two groups at baseline (TBM, 72(30)%: TIM, 86 (11)), although 2 patients in the TBM group had adherence in the poor range (<40%). Adherence at the end of the study in TIM and TBM groups were 89 (8) and 65 (33)% respectively (Fig. 2). Thus, adherence was maintained in the TIM group but declined in patients allocated TBM by >5%.

There were no changes in lung function or any other clinical parameter between the two groups. Low FVC measurements did not prevent any patient from using TIM.

3.3. Patient preference questionnaire

100% patients completely agreed or agreed with the statement that 1) TIM was very easy to understand, 2) very easy to use and 3) they were able to use it straight away. All patients randomised to TIM preferred its use to TBM aerosol delivery. There were no adverse events or patient withdrawals.

4. Discussion

For children with CF the use of target inhalation mode resulted in a reduction in the average time to complete a nebulised treatment during this study period of 8 weeks.

Table 1
Patient characteristics at baseline.

	TIM	TBM
Gender: male / female	7 / 3	7 / 3
Median (range) Age (years)	11.7 (8.7–15.9)	10.6 (5.2–16.9)
Median (range) FEV1 (% predicted)	74 (60–105)	80 (53–100)
Median (range) FEV1 litres/min	1.8 (1.2–3.9)	1.8 (1.1–3.0)
Median (range) FVC (% predicted)	94 (59–107)	89 (54–109)
Median (range) FVC litres/min	2.2 (1.7–4.7)	2.2 (1.3–4.3)
Median (range) Schwachman score	85/100 (65–95)	88/100 (60–100)
Median (range) CXR score	4/20 (2–9)	4/20 (1–12)
Median (range) number of treatments/day	2(1–3)	2(1–2)
Mean (SD) duration (months) of AAD TBM therapy prior to study	42.2(10.4)	34.7(12.5)

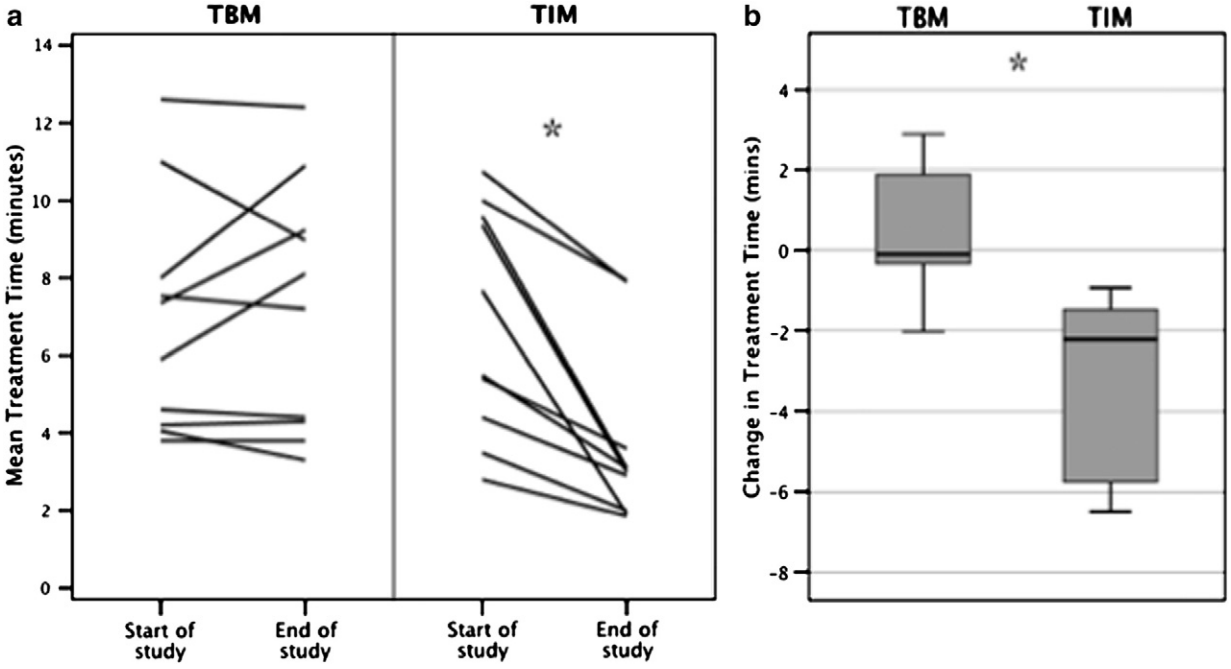

Fig. 1. a) Line graph showing individual changes in treatment times (minutes) for patients in TBM and TIM groups. Paired treatment times significantly decreased between the start and the end of the study period for patients allocated TIM but not TBM. b) Boxplot showing change in treatment times over the study period. Treatment times decreased in the TIM group by over 2 min but remained the same in patients allocated TBM ($p < 0.0001$).

Adherence was maintained in children using TIM system but declined in patients using the standard TBM. There was no difference in lung function between the two groups. Patients randomized to TIM preferred this mode to TBM and all patients opted to continue with TIM after the study period. These results support preliminary data examining single

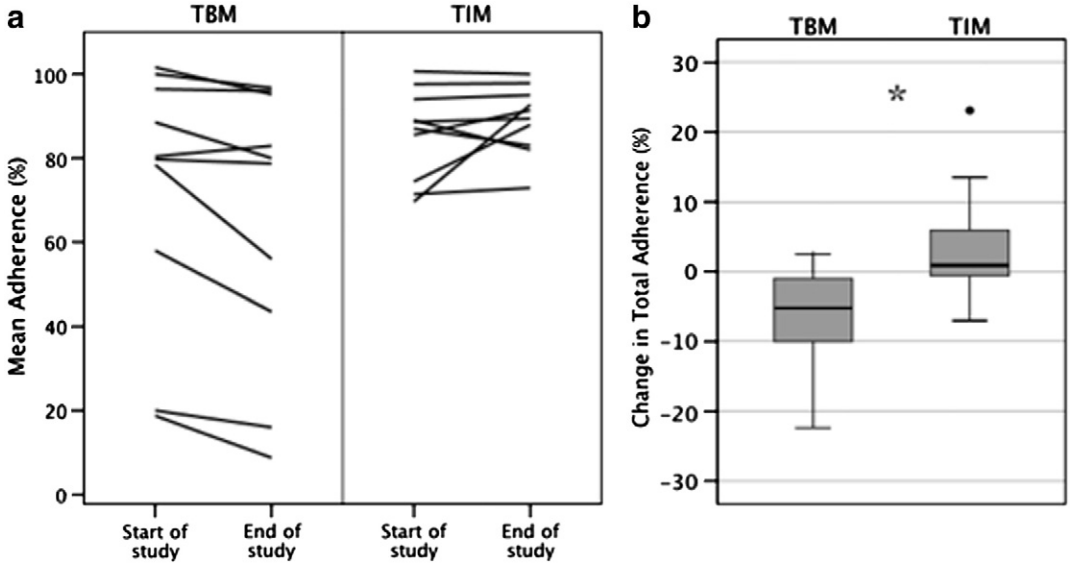

Fig. 2. a) Line graph showing individual changes in adherence (%) for patients in TBM and TIM groups. Overall, adherence was not significantly different during the baseline period between the two groups, despite the two poorly adherent patients in the TBM group. b) Boxplot (with outlier) showing change in adherence (%) following randomisation to TBM or TIM. Adherence declined in patients allocated TBM by approximately 5% but was maintained in the TIM group (*$p = 0.012$).

treatment episodes in adult patients with CF and are consistent with previous open assessments of this strategy, which are reassuring with respect to lung deposition.[9,10,13].

We expected TIM to have an impact on average treatment time, however the extent of this reduction was more than anticipated. We suspected that younger patients may find the technique of generating prolonged inspirations a challenge. Evidently, this was not the case and in most the reduction in treatment time was impressive. The reduction was marked in three patients but consistent across the group, in contrast to the TBM group (Fig. 1). We did not anticipate a difference in treatment adherence given the short study period and the fact that all children were established on their nebuliser regimen before entry into the study. This was a positive result in favour of the intervention; however the open-label nature of the RCT may have had an impact on this. Although the Research Physiotherapist did encourage all patients following randomization, it was inevitable that patients allocated TBM were disappointed. They did not have the novelty of a new breathing mode and, in retrospect, it was probably not surprising that adherence levels waned in the TBM group. Similarly this open-label study design may be criticized given that some technique training was required for the new breathing mode, however this reflects the real life situation and we did not feel it appropriate to provide training for a breathing mode that the TBM group would not use.

The CF patient demonstrating the largest reduction in treatment time was a 15 year old with Aspergers Syndrome. Using TIM, average treatment times reduced from 9.6 to 3 minutes. Parents reported this was a result of the direct feedback through the vibrating mouthpiece, which enabled the patient to focus on the breathing pattern.

We have previously reported on variability in treatment times between individuals.[5] In children, this relates to some degree on age and tidal volume. Adaptive aerosol delivery requires active participation from the patient and the device will not deliver aerosol unless the patient is breathing in a steady and regular manner. For some patients, this may lead to longer treatment times if they use the device in an erratic manner, for example if distracted. However, the volume of drug delivered to the lower airways does not vary significantly as the device will only deliver during appropriate inspiratory cycles.

These results have had a direct impact on our practice. We now advocate TIM for all patients on chronic suppressive therapy and also for patients with a new growth of *Pseudomonas aeruginosa* when we are attempting eradication. Reducing treatment times is a major benefit to patients and their families. Longer-term studies are needed to determine if these improvements in treatment times can be maintained.

This is a new era of aerosol delivery and novel advances in medical devices need to be monitored and assessed rigorously, [14] particularly as new and potentially expensive therapies emerge from translational studies. [14] Electronic data capture enables CF teams to work in an open partnership with patients to achieve the common goals of improving drug delivery and reducing patient burden.

Acknowledgements

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Appendix A. Study schedule

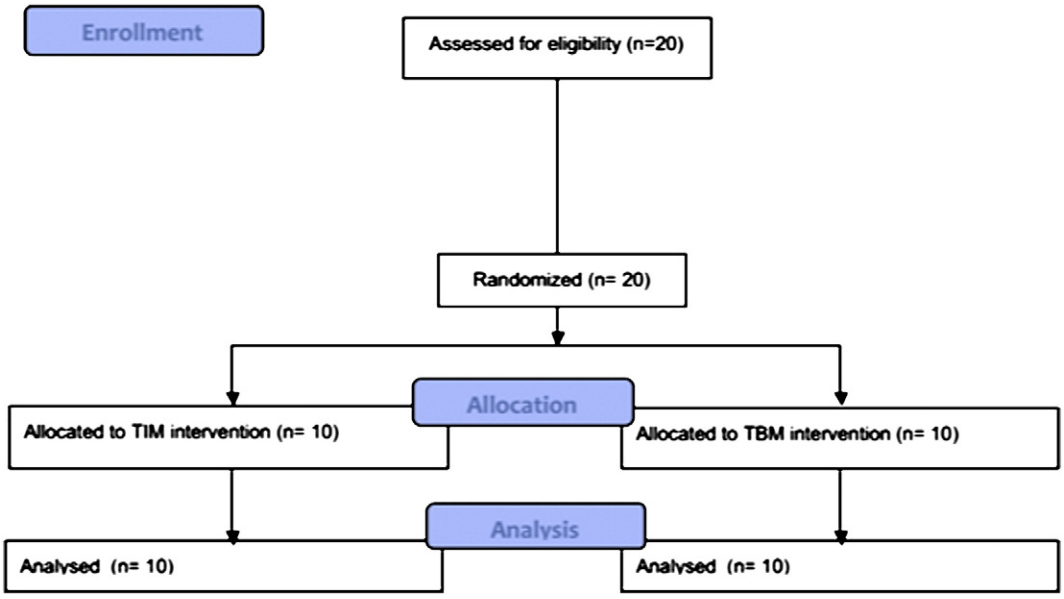
	Screening / visit 1	Visit 2 @ 4 weeks	Visit 3 @10 weeks
Written informed consent	✓		
Demographic information	✓		
Recent medical history	✓	✓	✓
Medication	✓	✓	✓
Physical examination	✓	✓	✓
Pulmonary function tests	✓	✓	✓
Sputum sample/ cough swab	✓	✓	✓
Issue new chamber set/mesh plate	✓		
Breathing monitor training	✓		
Adverse events		✓	✓
Download AAD	✓	✓	✓
Randomisation		✓	
Issue TIM mouthpiece and teach use (If randomised to TIM)		✓	
Administer test dose Colistin via TIM (If randomised to TIM)		✓	
Offer TIM to patients randomised to TBM in study and teach use			✓
Patient preference questionnaire (If randomised to TIM)			✓

Appendix B

TIM study.
Patient preference survey.
Please tick one answer for each statement.

1. My child found the TIM mouthpiece very easy to understand				
Completely Agree	Agree	Neither agree nor disagree	Disagree	Completely disagree
2. My child found the TIM mouthpiece very easy to use				
Completely Agree	Agree	Neither agree nor disagree	Disagree	Completely disagree
3. My child was able to use the TIM mouthpiece straight away				
Completely Agree	Agree	Neither agree nor disagree	Disagree	Completely disagree
4. My child took several days to get used to the TIM mouthpiece				
Completely Agree	Agree	Neither agree nor disagree	Disagree	Completely disagree
5. My child never got used to the TIM mouthpiece				
Completely Agree	Agree	Neither agree nor disagree	Disagree	Completely disagree
6. My child prefers the TIM mouthpiece to the standard mouthpiece				
Completely Agree	Agree	Neither agree nor disagree	Disagree	Completely disagree

Appendix C. Consort Flow diagram of enrollment and treatment allocations



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